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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,084	05/24/2000	Keiya Ozawa	50026/012002	5150

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,084	OZAWA ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10 and 14-24* is/are pending in the application.

4a) Of the above claim(s) *9 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10,14-18, and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 4-10 and 14-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location and the examiner of your application in the PTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Zachary C. Howard, Art Unit 1646, Technology 1600.

Status of Application, Amendments and/or Claims

The amendment of 9/16/05 has been entered in full. Claims 5, 8, 10, 15-18 and 20 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 9 and 19 remain withdrawn because they are directed to an invention nonelected with traverse in Applicant's response filed 7/14/03.

Claims 1, 4-8, 10, 14-18, 20-24 are under consideration in the instant application.

Priority

There is no written support for the currently claimed invention in the parent application 09/142,305. The '305 application does not mention fusion proteins comprising c-mpl. Therefore, the current application merits priority as of its filing date, 5/24/2000. This statement of priority was set forth at pg 2 of the 3/14/05 Office Action. Applicants in the 9/16/05 response do not provide any arguments to the contrary.

Specification

The Examiner notes that the specification has been amended to capitalize the trademarks found on pages 16, 22, 29 and 34, and to provide generic terminology to accompany the trademark.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (3/14/05).

The rejection of claims 8 and 18 under 35 U.S.C. § 101, first paragraph at pg 3 for being directed to non-statutory subject matter is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 17 under 35 U.S.C § 112, second paragraph, at pg 4 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims. However, please see the new rejection of claims 10, 14-18, 20 and 24 under 35 U.S.C. § 112, second paragraph necessitated by Applicants' amendments to the claims.

The rejection of claims 5, 9, 15-17 and 20 under 35 U.S.C § 112, second paragraph, at pg 4 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims that removed the confusing quotation marks.

The rejection of claims 1, 4, 6-8, 20 and 23 under 35 U.S.C. 103(a) as being unpatentable over Gurney et al in view of Wang et al is *withdrawn* upon further consideration of the references. The reference of Wang teaches only that the estrogen receptor forms dimers and does not provide motivation to fuse the estrogen receptor to heterologous proteins; this is highlighted by the fact that it was necessary to cite Jackson et al in the 3/14/05 Office Action in support of the rejection. Please note that the rejection of the same claims as being unpatentable over Gurney et al in view of Jackson et al is *maintained* (see below). All of Applicants' pertinent arguments made in response to the rejection over Gurney in view of Wang are answered below in so far as they apply to the Gurney in view of Jackson rejection.

Please see new claim rejections below.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 10, 14-18, 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 10, as amended 9/16/05, is directed to a vector comprising a gene and a DNA, wherein the gene and DNA are located on the same or different molecules. The term vector, as used in the art and the instant specification, refers to a single vector molecule. However, the vector of claim 10 encompasses a single vector comprising multiple molecules ("different molecules"). The specification at pg 7-8 teaches, "the vector used in the present invention includes not only a single vector...but also includes a vector system of multiple vector molecules..." While the specification describes a vector system comprising multiple vector molecules, there is no description of a single vector comprising multiple molecules, nor does the concept flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for "a vector" comprising multiple molecules. The remaining claims depend from claim 10 and therefore contain new matter for the same reason as claim 10.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 10, 14-18, 20 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because it is unclear whether the claim is encompasses single or multiple vectors. The term vector, as used in the art and the instant specification, refers to a single vector molecule. Therefore, it is unclear how the vector of claim 10 can comprise a gene and a DNA, "wherein said exogenous gene and said DNA...may be located...on different molecules". The specification at pg 8, teaches, "a vector system of multiple vector molecules comprising..." This claim would be rendered definite if amended to recite, for example, "A vector system comprising..."

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

Claims 1, 4, 6-8, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney et al in view of Jackson et al for the reasons set forth in the 3/14/05 Office Action.

Applicants' arguments (9/16/05) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 9/16/05, Applicants submit that at the time the invention was made one could not have reasonably predicted that the modifications proposed by the Office would yield a functional fusion protein. Applicants point to MPEP 2143.02 (citing *In re Merck*) as stating that there must be a reasonable expectation of success to combine prior art references to reject claims as prima facie obvious. Applicants submit that the Gurney teaches a chimeric receptor, comprised of the extracellular domain of the human growth hormone receptor (GHR) and the intracellular domain (i.e., proliferation inducing domain) of c-mpl, that retains the proliferative and cell signaling activities of the native c-mpl receptor. Applicants submit (and point to Gurney as teaching) that c-mpl and GHR are both members of the cytokine receptor superfamily that despite lacking significant sequence identity possess similar functional architecture (e.g., both are single pass plasma membrane proteins) and functionality (e.g., both homodimerize and signal through the JAK/STAT pathway). Applicants submit that in view of Gurney one would not expect that a fusion protein comprised of two divergent receptor components would similarly maintain its functionality. Applicants submit that because GHR and c-mpl possess structural similarity, one would reasonably expect that replacing the ligand binding domain of another cytokine receptor (similar to GHR) would yield a functional receptor; but replacing the ligand binding domain with a non-cytokine receptor (e.g., the estrogen receptor) would not yield a functional receptor. Applicants submit that steroid hormone receptors (e.g., estrogen receptor) are intracellular (or nuclear) receptors, confined exclusively to the cytosol and nucleus. Applicants submit that the two protein families have substantially different structures as

well as divergent ligand binding and signal transduction mechanisms. Applicants submit the dimers formed by GHR and ER are dramatically different in terms of structure, composition, activity, and nature of ligand bound.

Applicants' arguments have been fully considered but are not found persuasive. The Examiner does not dispute that GHR and ER have substantially different structures and signaling mechanisms. However, both receptors share the ability to dimerize in response to specific ligand binding, and retain this quality when bound to heterologous proteins. Jackson teaches that at the time the invention was made that estrogen receptors were useful when fused to a wide variety of heterologous proteins. Furthermore, Jackson fuses the estrogen receptor to the entire c-abl protein. As noted above, in the section entitled "Priority", the claimed invention including c-mpl merits priority only to the filing date of 5/24/2000. The relevant art at the time the invention made supports Jackson's teachings that ER-HBD has wide applicability, including receptors. For example, Ito et al, 1997 teaches fusion of the ER-HBD to the C-terminus of the granulocyte colon-stimulating factor receptor (Ito et al. 1997. Blood. 90(10): 3884-3892). Ito teaches, "The strategy used in the present study is based on the finding that estrogen can activate fusion proteins between ER-HBD and a wide variety of heterologous proteins" (pg 3888) and that the HBD is a "dimerization domain" (pg 3888). A HBD review teaches, "The subcellular location is primarily determined by the heterologous moiety" (see pg 269 of Picard, Ch 11 (pg 261-274) in Nuclear Receptors: a Practical Approach (D. Picard, ed) Oxford University Press, Oxford, 1999).

In the response dated 9/16/05, Applicants further submit that one skilled in the art would not have a reasonable expectation of success. Applicants submit Jackson describes fusion proteins of c-abl, which is a non-receptor-type tyrosine kinase whose signal transduction occurs after ligand binding, the inductive signals and mechanisms associated with c-abl were less defined than c-mpl. Applicants argue that the fact that c-abl was not activated by other dimerizing receptors and that dimerization is not generally seen in non-receptor type molecules suggests that the activation process involves another mechanism, such as the association with a heat shock protein (HSP90). Applicants submit that Jackson's findings were of unique and unexpected

nature that does not support that all dimerizing receptors are interchangeable equivalents.

Applicants' arguments have been fully considered but are not found persuasive. The Examiner does not dispute that the activation mechanisms of c-abl were less well defined than c-mpl. The Examiner does not dispute that Jackson teaches that C-terminal fusion of the estrogen receptor hormone-binding domain (ER-HBD) activated c-abl while C-terminal fusion of Gag, Bcr or the ecdysone receptor did not. However, Jackson does not characterize the activation process as occurring due to association with HSP90. Rather, Jackson hypothesizes that inactivation of the Abl receptor might be due to association with HSP90 (see pg 2817, left column). With regard to activation by fusion to ER-HBD, Jackson considers two hypothesis, oligomerization and overexpression (see pg 2817-2818). Jackson teaches, "overexpression is not sufficient for transformation" (see pg 2818). Jackson teaches that the prior art considered dimerization to be a plausible mechanism for activation by ER-HBD fusion: "The suggested ability of the HBD to promote hormone-dependent dimerization would provide a mechanism for activation" (pg 2817). Jackson does not provide any direct evidence of dimerization but clearly considers it the best hypothesis. Therefore, at the time the state of art would support that the ER-HBD had the ability to form dimers. With regard to Applicants' characterization of Jackson's findings were unique, Applicant is disregarding the teachings of Jackson in regard to the broad applicability of the ER-HBD fusion (pg 2818). To quote Jackson, "The extension of regulation-by-fusion to an HBD from transcription factors to kinases suggests that this strategy may provide regulable alleles for a variety of regulatory and enzymatic moieties, including gene products of unknown biochemical function" (pg 2818).

Applicants further submit that combining the references would result in a non-functional chimera. Applicants submit that the estrogen would not be a useful substitution for the GHR as taught by Gurney et al because one skilled in the art would have simply replaced the ligand binding domain of the growth hormone receptor with the ligand binding domain of the estrogen receptor, thereby yielding a fusion protein containing the ER HBD and intracellular domain of c-mpl. Applicants point to

Nagashima (2003) and submit that they have discovered that simple fusion of a receptor with ER does not automatically lead to activation but rather the tertiary structure of the extracellular domain is critical. Applicants submit that deletion of regions of the extracellular region of c-mpl abolished reactivity to both TPO and estrogen. Therefore, Applicants submit that the proposed modification of Jackson would render the prior art invention of Gurney unsatisfactory for its intended purpose, and therefore as there can be no suggestion of motivation to make the proposed modification.

Applicants' arguments have been fully considered but are not found persuasive. The Examiner does not dispute Applicants' findings that a fusion protein comprising deletions of the extracellular domain result in a non-functional chimera. However, Gurney in view of Jackson renders obvious fusions of the entire c-mpl protein with estrogen, including the entire extracellular domain. Jackson makes fusions to the entire c-abl protein. Gurney teaches both GH-c-mpl fusions and discusses full-length c-mpl as it was known in the art (see pg 5296). Jackson merely provides the motivation to substitute the ability of ER-HBD to dimerize for the ability of GHR to dimerize. However, in doing so one would want to retain the membrane association of c-mpl because Gurney teaches "A region of the c-mpl intracellular domain proximal to the cell membrane is necessary and sufficient to transmit a proliferative signal [emphasis added]" (pg 5295). If one were substituting ER-HBD for GHR, one would clearly recognize that this intracellular domain needed to remain proximal to the cell membrane. Therefore, when constructing ER-HBD-c-mpl fusion, it would be obvious to use the full-length c-mpl receptor with ER-HBD fused to the c-terminus to render c-mpl responsive to estrogen, but also retain the membrane association of c-mpl.

Claims 1, 4-8, 10, 14, 15, 17, 18, 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al, 1997 (Blood. 90(10): 3884-3892) in view of Gurney et al, 1995 (Proc Natl Acad Sci USA. 92: 5292-5296, first cited in the 10/31/03 Action).

Ito teaches a fusion protein comprising the hematopoietic cytokine receptor G-CSF and the estrogen receptor hormone-binding domain (Fig. 1a; pg 3886) that is

functional in proliferation of murine bone marrow cells (pg 3888). Ito teaches DNA, vectors and isolated cells encoding the fusion protein (pg 3885). Ito teaches a vector system comprising the exogenous gene *bsr* and the DNA encoding the fusion protein (separate molecules that are co-transfected). Ito teaches a mutant ER gene that binds synthetic 4-hydroxytamoxifen but not estrogen and teaches the advantage of using this mutant ER in the fusion protein of the invention (pg 3891).

Therefore, Ito teaches all of the limitations of the claims, except that the fusion proteins comprise c-mpl, or a proliferation inducing part of c-mpl.

Gurney teaches that c-mpl is a "member of the hematopoietic cytokine receptor family" (see Abstract). Gurney teaches that ligand of c-mpl is thrombopoietin which is responsible for "stimulating the proliferation and maturation of megakaryocytes". Gurney further teaches fusion proteins comprising the extracellular domain of growth hormone receptor and the cytoplasmic proliferation domain of c-mpl.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute either full-length c-mpl as taught by Gurney, or the cytoplasmic domain of c-mpl, as taught by Gurney in the fusion protein taught by Ito.

The person of ordinary skill in the art would be motivated to do so in order to use the fusion protein to selectively amplify megakaryocyte cells. The person of ordinary skill in the art would have expected success because Ito teaches all of the techniques necessary to make the fusion protein and use it for proliferation of hematopoietic cells. One would substitute either full-length c-mpl, or just the cytoplasmic domain, because Gurney teaches that either is sufficient for proliferation, and Gurney further teaches that fusions of the cytoplasmic domain to the extracellular domain of another cytokine receptor are functional.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4 and 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 and 4 of copending Application No. 09/142305 in view of Solar et al, 1998 (Blood. 92(1): 4-10).

As noted above in the section titled "Priority", the instant application is a CIP of 09/142305 and claims priority to the filing date of 09/142305. However, the disclosure of 09/142305 does not disclose the fusion proteins comprising c-mpl. Therefore, with regard to the species of c-mpl, the instant application does not merit priority to the disclosure of 09/142305.

It is noted that the claims of application 09/142305 were last amended 9/26/05.

Claims 1, 3 and 4 of '305 contain all of the limitations of claims 1, 4 and 23 of the instant application, except that the second polypeptide is limited to the G-CSF receptor in '305 and to c-mpl in the instant application.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute either full-length c-mpl as taught by Gurney, or the cytoplasmic domain of c-mpl, as taught by Gurney in the fusion protein taught by Ito.

The person of ordinary skill in the art would be motivated to do so in order to use the fusion protein to selectively amplify megakaryocyte cells. The person of ordinary

skill in the art would have expected success because Ito teaches all of the techniques necessary to make the fusion protein and use it for proliferation of hematopoietic cells. One would substitute either full-length c-mpl, or just the cytoplasmic domain, because Gurney teaches that either is sufficient for proliferation, and Gurney further teaches that fusions of the cytoplasmic domain to the extracellular domain of another cytokine receptor are functional.

This is a provisional obviousness-type double patenting rejection.

Claims 6-8, 10, 14, 17, 18, 20 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 and 4 of copending Application No. 09/905592 in view of Solar et al, 1998 (Blood. 92(1): 4-10).

The '592 application is a divisional application of copending Application No. 09/142305. As noted above in the section titled "Priority", the instant application is a CIP of 09/142305 and claims priority to the filing date of 09/142305. However, the disclosure of 09/142305 does not disclose the fusion proteins comprising c-mpl. Therefore, with regard to the species of c-mpl, the instant application does not merit priority to the disclosure of 09/142305.

It is noted that the claims of application 09/905592 were last amended 11/7/05.

Claims 8, 12, 14, 15, 17 and 18 of '305 contain all of the limitations of claims 6-8, 10, 14, 17, 18, 20 and 24 of the instant application, except that the vector is limited to one encoding the G-CSF receptor in '305 and to c-mpl in the instant application.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute either full-length c-mpl as taught by Gurney, or the cytoplasmic domain of c-mpl, as taught by Gurney in the fusion protein taught by Ito.

The person of ordinary skill in the art would be motivated to do so in order to use the fusion protein to selectively amplify megakaryocyte cells. The person of ordinary skill in the art would have expected success because Ito teaches all of the techniques necessary to make the fusion protein and use it for proliferation of hematopoietic cells. One would substitute either full-length c-mpl, or just the cytoplasmic domain, because

Gurney teaches that either is sufficient for proliferation, and Gurney further teaches that fusions of the cytoplasmic domain to the extracellular domain of another cytokine receptor are functional.

This is a <u>provisional</u> obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER